Remarks

Claims 1-8 were pending in the application. In accordance with the Response to the Restriction Requirement dated May 8, 2006, claims 1 and 4 were elected with traverse and claims 2, 3 and 5-8 were withdrawn. Claims 1 and 4 are now pending in the application. Claims 1 and 4 are rejected. Claims 1 and 4 are also objected to, new claims 9-11 are added, and no claims were allowed. By the foregoing amendment, claims 2, 3 and 5-8 are withdrawn, claims 1 and 4 are amended, and new claims 9-11 are added. No new matter is presented.

Oath/Declaration

The Examiner indicated the Oath or Declaration is defective. The oath does not list the foreign priority document, France 98/15074 under 35 U.S.C. §119(a)-(d). A new oath or declaration in compliance with 37 C.F.R. §1.67(a) identifying the application by application number and filing date is required. See MPEP §§602.01 and 602.02.

Applicants submit herewith a new Oath/Declaration that lists the foreign priority document, France 98/15074, in compliance with 37 C.F.R. §1.67(a).

Applicants respectfully request the Examiner withdraw the objection to the Oath/Declaration and find the Oath/Declaration complies with the statutory requirements under 37 C.F.R. §1.67(a).

Specification

The Examiner objected to the specification due to informalities.

Applicants intend to submit a Supplemental Response along with copies of a marked-up Substitute Specification and a clean Substitute Specification to address the informalities.

Drawings

The Examiner objected to Figures 1, 2, 6, 11, 12, and 15 due to informalities.

Applicants intend to submit a Supplemental Response along with substitute sheets of formal drawings of Figures 1, 2, 6, 11, 12, and 15 to address the informalities.

Objections to Claims 1 and 4

The Examiner objected to claims 1 and 4 because the claims contain recitation of non-elected inventions, formulas (I) and (III).

Applicants have amended claims 1 and 4 to remove the recitation of non-election inventions, formulas (I) and (III).

In light of the foregoing, Applicants respectfully request the Examiner withdraw the objection and find claims 1 and 4 allowable.

Claim Rejections-35 U.S.C. §101

The Examiner asserts claims 1 and 4 are rejected under 35 U.S.C. §101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process under 35 U.S.C. §101. Applicants respectfully traverse the rejection.

Applicants have submitted new claims 9-11 directed to methods for diagnosis of a Central Nervous System (CNS) disease, for treatment of a Central Nervous System (CNS) disease, and for driving a substance across the Blood Brain Barrier (BBB) to the Central Nervous System (CNS), respectively.

Applicants submit herewith an Information Disclosure Statement under 37 C.F.R. §1.97 containing several articles referenced throughout the following discussion. In an effort to provide the Examiner a better understanding of the subject matter recited in new claims 9-11, Applicant submits articles pertaining to the use of linear peptides to enable the transport of various active molecules across the Blood Brain Barrier (BBB).

1) Brain transport of small molecules

The efficacy of linear peptides to enhance the brain uptake of the anti-cancer agent doxorubicin was assessed using *in situ* cerebral perfusion in rats (Rousselle, C., et al. New advances in the transport of doxorubicin through the blood-brain barrier by a peptide vector- mediated strategy. *Mol Pharmacol.*, 57, 679, 2000.) and mice (Rousselle, C., et al. Enhanced delivery of doxorubicin into the brain via a peptide-vector-mediated strategy: saturation kinetics and specificity. *J Pharmacol. Exp Ther.*, 296, 124, 2001).

In the first article, the inventors demonstrate in Figure 3 (page 682) that coupling doxorubicin with SynB1 vector enhances significantly its brain uptake. The second article shows that the enhancement is also observed in mice with the following peptide vectors: SynB1, SynB3 and its enantiomer D-SynB3 (Figure 3, page 127).

In another study, the inventors have coupled anticancer agent paclitaxel with SynB3 vector via a succinate linker (Blanc, E., et al. Peptide-vector strategy bypasses P-glycoprotein efflux, and enhances brain transport and solubility of paclitaxel. *Anticancer Drugs.*, 15, 947, 2004). Figure 3 (page 952) demonstrates that although paclitaxel is very lipophilic, we only observed a low brain uptake of paclitaxel. In contrast, its coupling to SynB3 resulted in a significant increase in paclitaxel brain uptake.

Similar enhancement in brain uptake was obtained with another small molecule: the antibiotic benzyl-penicillin (B-Pc). B-Pc was coupled to SynB1 vector via an ester linker and the brain uptake was measured using *in situ* brain perfusion (Rousselle, C., et al. Improved Brain Delivery of Benzylpenicillin with a Peptide-Vector-Mediated Strategy. *J Drug Target.*, 10, 309, 2002). The brain uptake of coupled B-Pc showed an average of 8-fold increase in comparison to free B-Pc (Figure

3, page 313). This increase was quite similar for the seven explored gray areas of the rat brain (Figure 2, page 312). The inventors have also shown that vectorisation of morphine-6-glucuronide (M6G), by SynB3 can enhance its brain transport (Temsamani, J., et al. Improved brain uptake and pharmacological activity profile of morphine-6-glucuronide using a peptide vector-mediated strategy. *J Pharmacol Exp Ther.*, 313, 712, 2005). M6G is an active metabolite of morphine and was shown to have a poor brain uptake. Vectorisation of M6G with the SynB3 vector (Syn1001) resulted in a significant improvement in the brain uptake (see paragraph BBB permeability, page 715). Interestingly, this increase in brain uptake was accompanied by an enhancement in the analgesic activity of M6G (Figure 1B &C, page 715 and Figure 2 & 3, page 716).

2) Brain Transport of Peptides and Proteins

In a pharmacological application focused on pain management, the brain uptake of an enkephalin analogue dalargin was enhanced significantly after vectorisation (Rousselle, C., et al. Improved brain uptake and pharmacological activity of dalargin using a peptide-vector mediated strategy. *J Pharmacol Exp Ther.*, 306, 371, 2003). We have shown by *in situ* brain perfusion that vectorisation with SynB1 and SynB3 vectors markedly enhance the brain uptake of dalargin (Figure 3, page 374). Free or conjugated dalargin were also administered intravenously to mice and anti-nociception was determined using the Hot plate test, an assay known to measure the analgesic activity. The results show that intravenous administration of dalargin to mice exhibited no analgesic activity; while conjugation of dalargin to SynB vectors led to a considerable enhancement of analgesic activity immediately after the intravenous injection (Figure 4, page 374).

In another application the inventors demonstrated that SynB vectors are able to transport large molecules, such as the protein streptavidin (M.W. approx. 60,000 Da), across the BBB (Temsamani & Scherrmann Peptide vectors as drug carriers. Prog

Drug Res. 2003;61 :221-38). Streptavidin was attached to a biotin moiety linked to the peptide vector. *In situ* brain perfusion studies in mice showed that attachment of SynB vector to streptavidin resulted in about 30-fold enhancement in brain uptake (Figure 6, page 203).

Claim Rejections-35 U.S.C. §112, first paragraph

The Examiner asserts claims 1 and 4 are rejected under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse the rejection.

Applicants have submitted new claims 9-11 directed to methods for diagnosis of a Central Nervous System (CNS) disease, for treatment of a Central Nervous System (CNS) disease, and for driving a substance across the Blood Brain Barrier (BBB) to the Central Nervous System (CNS), respectively.

Applicants respectfully request the Examiner refer to the articles submitted in the Information Disclosure Statement submitted herewith and the comments set forth above.

Claim Rejections-35 U.S.C. §112, second paragraph

The Examiner asserts claims 1 and 4 are rejected under 35 U.S.C. §112, second paragraph. Applicants respectfully traverse the rejection.

Applicants have submitted new claims 9-11 directed to methods for diagnosis of a Central Nervous System (CNS) disease, for treatment of a Central Nervous System (CNS) disease, and for driving a substance across the Blood Brain Barrier (BBB) to the Central Nervous System (CNS), respectively.

Applicants respectfully request the Examiner refer to the articles submitted in the Information Disclosure Statement submitted herewith and the comments set forth above.

Conclusion

Accordingly, Applicant submits that claims 1, 4 and 9-11 are in condition for allowance. Please charge any fees or deficiency or credit any overpayment to our Deposit Account of record.

Respectfully submitted,

By _____
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Date: November 30, 2006

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: "Mail Stop Amendment, Commissioner for Patents, Washington, D.C. 20231" on November 30, 2006.

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Ross Christie